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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/978,637	11/25/1997	ELAZAR RABBANI	Enz-53(D5)	4643

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
03/09/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	08/978,637	RABBANI ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1-24-11*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *318-323* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *265,268,270,272,284,290,296,299,303,304,308,312,313,325 and 326* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 265,268,270,272,284,290,296,299,303,304,308,312,313,318-323,325 and 326.

DETAILED ACTION

This Office action is in response to the communication filed 1-24-11.

Claims 265, 268, 270, 272, 284, 290, 296, 299, 303, 304, 308, 312, 313, 318-323, 325 and 326 are pending in the instant application.

Claims 318-323 have been withdrawn as being drawn to a non-elected invention.

Claims 265, 268, 270, 272, 284, 290, 296, 299, 303, 304, 308, 312, 313, 325 and 326 have been examined on their merits as set forth below.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1-24-11 has been entered.

Response to Arguments and Amendments

Applicant's arguments with respect to claims 265, 268, 270, 272, 284, 290, 296, 299, 303, 304, 308, 312, 313, 325 and 326 have been considered but are moot in view of the new ground(s) of rejection set forth below.

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

New Rejections Necessitated by Amendments

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 265, 268, 270, 272, 284, 290, 296, 299, 303, 304, 308, 312, 313, 325 and 326 are rejected under 35 U.S.C. 103(a) as being unpatentable over Izant (Chimeric Antisense RNAs, in Gene Regulation: Biology of Antisense RNA and DNA, pages 183-195 (Erickson, R.P and Izant, J.G., eds.; Raven Press, Ltd: New York) (1992), Frankel et al (USPN 5,989,814), and Zieve et al (Critical Rev. in Biochem. & Molec. Biol., Vol. 25, No. 1, pages 1-46, 1990), the combination in view of Meador et al (USPN

5,547,862), Dahlberg et al (The Genes & Transcription of the Major Small Nuclear RNAs, *in* Structure and Function of Major & Minor Small Nuclear Ribonucleoprotein Particles, pages 38-70, Max L. Birnstiel, Ed., Springer-Verlag: New York, 1988), Calabretta et al. (USPN 5,734,039) and Binkley et al (Nucleic Acids Research, 1995, Vol. 23, No. 16, pages 3198-3205), the combination further in view of Craig et al (WO 95/08635) and Alul et al (USPN 5,532,130).

The claims are drawn to isolated nucleic acid constructs which act as templates for the synthesis of a nucleic acid comprising a nuclear localization sequence comprising a portion of U1, U2 or U4 SnRNA, which portion comprises sequences for at least two stem loops present at the 3' end of native U1, U2 or U4 snRNA and a reimportation signal, and further comprising an antisense which replaces stem-loop sequence removed from the U1, U2 or U4 snRNA that are not in said two stem loops present at the 3' end of the snRNA, wherein the NLS comprises a portion of U1 RNA comprising C and D loops, which constructs optionally comprises multi-cassette constructs comprising at least three copies of a promoter which produces nucleic acids specific for each promoter in a eukaryotic cell, and which with specific nucleic acids specifically target viral RNAs or viral proteins in a cell, which virus is optionally HIV.

Izant (Chimeric Antisense RNAs, in Gene Regulation: Biology of Antisense RNA and DNA, pages 183-195 (Erickson, R.P and Izant, J.G., eds.; Raven Press, Ltd: New York) (1992) isolated nucleic acid constructs which act as templates for the synthesis of a nucleic acid comprising a nuclear localization sequence comprising a portion of U1, U2 or U4 SnRNA, which portion comprises sequences for at least two stem loops

present at the 3' end of native U1, U2 or U4 snRNA and a reimportation signal, and further comprising an antisense which replaces the stem-loop sequence removed from the U1, U2 or U4 snRNA that are not in said two stem loops present at the 3' end of the snRNA, wherein the NLS comprises a portion of U1 RNA comprising C and D loops, (see entire document, esp. pages 183-184; 186-190).

Frankel et al (USPN 5,989,814) also teaches the nuclear localized sequence located in the U1 RNA (see esp. Figure 2).

Zieve et al (Critical Rev. in Biochem. & Molec. Biol., Vol. 25, No. 1, pages 1-46, 1990) teach the structure and function of U1, U2 or U4 snRNA, the sequences necessary for their transcription and nuclear retention (see entire article, esp. pages 1-4, 7-13, 17, 19, 20-21, and 24).

The primary references do not teach multicassette expression systems for the expression of antisense specific for HIV RNA, nor do they teach nucleic acids that bind to or target nucleic acids encoding HIV cellular proteins, nor nucleic acids that bind to decoy proteins.

Meador et al (USPN 5,547,862) teach cells and in vitro cultures comprising nucleic acid compositions comprising nucleic acid constructs comprising multiple cassettes, comprising a primary nucleic acid which is a template for the synthesis of a secondary nucleic acid which is a template for the synthesis of a gene product, and further comprises a signal processing sequence (See esp. the abstract, col. 1-3, 11, col. 15-17, claims 1-25).

Dahlberg et al (The Genes & Transcription of the Major Small Nuclear RNAs, *in* Structure and Function of Major & Minor Small Nuclear Ribonucleoprotein Particles, pages 38-70, Max L. Birnstiel, Ed., Springer-Verlag: New York, 1988) teach transcriptional units comprising U1, U2 and U4 snRNA, and teach the structure and function of these snRNA constructs, as well as the motivation to use the same, rather than different promoters in a multiple promoter construct (see esp. pages 39-40, 51-56, 58--61).

Calabretta et al teach a composition for introducing two different antisense oligonucleotides specific for two different genes to a cell. Calabretta teaches a nucleic acid construct targeting a cytoplasmic oncogene or proto-oncogene DNA, and a second segment targeting a nuclear oncogene or proto-oncogene. The DNA containing segments are in inverted orientation such that transcription of the DNA produces RNA complementary to the two mRNA transcripts of the two oncogene targets (see columns 8 and 9, for example). Calabretta teaches various modifications of the nucleic acids and means of delivery of the compositions.

Binkley et al teach high affinity RNA ligands to human nerve growth factor (NGF), which is a protein that is essential for growth, differentiation and maintenance of neurons and has the ability to localize or attract NGF-sensitive growing axons. Binkley teaches that the SELEX procedure is a widely used technique for isolating, identifying, and characterizing RNAs with high specificity and affinity to proteins, which target proteins may be optionally located in the nucleus or the cytoplasm. Binkley teaches that specific RNA ligands to proteins can be routinely generated and isolated using SELEX.

Craig et al teach the expression of viral decoy proteins under the control of a locus control region and teach that decoy proteins act as antagonists to natural proteins involved in the replication of the HIV virus. Craig teaches that a decoy protein can be used as a mutant of a transactivator protein that is capable of binding to the transactivator-responsive site on the host or viral genome, yet is incapable of activating transcription (see pages 2 and 3, for example).

Alul et al teach the routine experimentation and design of antisense or ribozymes to target HIV RNA encoding proteins (see esp. the second paragraph of the section entitled "Background of the Invention").

It would have been obvious to design a multi-cassette nucleic acid construct comprising the U1, U2, or U4 snRNP transcriptional constructs taught previously by Izant and Zeist, and comprising the nuclear localization domain taught by Frankel for expression of viral inhibitory constructs, and relying on the teachings of multiple promoter constructs taught previously by Meador because the elements required for producing such recombinant nucleic acids, including antisense and sense nucleic acids, using portions of the snRNAs as instantly claimed were well known in the art. One would have been motivated to design and utilize such nucleic acid constructs because they provide the flexibility of expressing multiple nucleic acids encoded by operably linked primary nucleic acids, including elements that allow for localization in different subcellular compartments, depending on where the target gene is located, including the well know nuclear localization binding domain of the snRNA. One would have reasonably expected that the inclusion of nuclear localizing or cytoplasmic localizing

signals in the particular cassette would allow for the expression of the operably linked nucleic acid in the corresponding subcellular component. One would have been motivated to use the same promoter in a multiple cassette because Dahlberg teach the competition between different promoters in a single expression cassette.

It would have been obvious to incorporate operably linked RNA oligonucleotides that bind to proteins, as taught by Binkley, or antisense oligonucleotides taught in the system of Calabretta et al or Izant. One would have been motivated to incorporate RNA oligonucleotides that bind to proteins instead of the antisense oligonucleotides in the multicomponent system taught previously by Meador because Binkley teaches that high affinity RNA ligands can be produced that specifically bind to proteins, and can be easily generated and isolated using the SELEX procedure.

One would have a reasonable expectation of success given that each of the nucleic acid molecules were known to bind with target molecules in a sequence specific manner, as evidenced by the teachings of Calabretta, Izant, Dahlberg, Zieve, and Binkley. One would have a reasonable expectation of success to express the protein binding RNA molecules of Binkley or the targeting system of Calabretta or Tan in the multi-cassette system of Meador, or alternatively swapping the multi-cassette promoters of Meador with the snRNA promoters taught previously by Izant, Zieve or Dahlberg with the advantage of producing two, three or more different inhibitory or binding molecules at once, and optionally in different parts of the cell, depending on the location of the corresponding target gene.

It also would have been obvious to use the SELEX method to assay for RNA molecules that bind to a protein, as taught by Binkley and to specifically use a decoy protein as the protein, as taught by Craig. One of ordinary skill would have been motivated to design and synthesize antisense that target and inhibit the expression of HIV proteins to search for potential therapeutics to inhibit HIV infections, as taught previously by many in the art, including Alul et al. One would have been motivated to screen for resultant RNA aptamers against a decoy protein because Binkley teaches that high affinity RNA ligands to proteins can be easily isolated using the SELEX procedure and teach that such RNAs may furnish useful diagnostic tools for the study of proteins, or to regulate the actions of decoy proteins in a cell. Since teach that decoy proteins are proteins that are useful to serve as mutants capable of binding to a preferred site but yet incapable of activating transcription, one would have been motivated to use the SELEX method of Binkley. to identify RNA ligands to any known protein, such as the decoy proteins of Craig, or to screen for RNA ligands that localize and inactivate the decoy proteins in a cell.

One would have a reasonable expectation of success given that Izant and Calabretta teach the ability of antisense to bind and inhibit the expression of a target gene, Craig teaches the benefits of decoy proteins, and Binkley teach assaying for RNA aptamers using routine experimentation, and teach a method (SELEX) that is widely use to identify RNA molecules that bind to known proteins.

Thus, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is **571-273-8300**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** The examiner's office hours are generally Monday-Friday, 10:30am - 7pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Heather Calamita, can be reached on (571) 272-2876. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
3-7-11

/Jane Zara/

Primary Examiner, Art Unit 1635